Schizophrenia patients showed impaired hippocampal and prefrontal responses during associative learning: fMRI evidence of hypoactivation and dysplasticity

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Background: The hippocampus and the prefrontal cortex are involved in the encoding and retrieval of associations in memory (1). Both regions are of particular relevance in understanding the functional pathophysiology of schizophrenia as several studies suggest structural MRI and molecular impairments in them (2, 3). However, few studies in patient populations have applied tasks such as associative learning that specifically engage the hippocampus in the encoding, and the prefrontal cortex in the retrieval of associative memories (4). In this study we examined differences in hippocampal and dorso-lateral prefrontal fMRI activity between stable schizophrenia patients (SCZ) and healthy control subjects (HC) while subjects performed an associative learning task in which they learned the associations between nine unique objects and their locations in a spatial grid. Of particular interest were differences in the change in activity from baseline, changes in the pattern of activity as a function of learning and increases in behavioral proficiency.

Methods: fMRI was conducted using a 4T Bruker MedSpec with standard epi (TR=3 s, TA=1.5 s, TE=30 ms, 24 axial slices, 64 x 64 matrix). During learning subjects alternated between blocks of encoding, rest and retrieval. During encoding, nine equi-familiar objects were presented in sequential random order (3s/object) in grid locations for naming. Following a brief rest interval, memory for object-location associations was tested by cuing grid locations for retrieving objects associated with them (3s/cue). Object names were monosyllabic to minimize head motion. Eight blocks (each cycling between encoding, rest and retrieval) were employed. fMRI analyses (smoothing, detrending, normalization) were conducted using SPM2. Signal from a-priori defined bilateral regions of interest (hippocampus and middle frontal gyrus) were extracted using MarsBar (5, 6). Block wise signal changes in encoding and retrieval (relative to resting baseline) were computed for each subject. To date, nine subjects including five controls (HC, age=24 yrs, 3 males) and four stable schizophrenia patients (SCZ, age=28 yrs, 3 males) consented to participate.

Results: Behavioral performance across eight blocks conformed to negatively accelerated power functions ($y=1-e^{-kx}$)(7). The single free parameter k, a metric of learning rate was significantly lower in SCZ compared to HC (.31 vs. .51; t_7=4.01, p<.01), indicating slower associative learning. Mean percent signal change from the hippocampus (encoding) and the prefrontal cortex (retrieval) were submitted to two way (group, hemisphere) analyses of variance. Compared to HC, SCZ showed significantly reduced signal change in the hippocampus during encoding ($F_{1,14}$=13.65, p<.01), and marginally significant reductions in dorso-lateral prefrontal cortex during retrieval ($F_{1,14}$=3.1, p<.05; one-tailed). Blockwise changes in signal were analyzed for each group to assess patterns of adaptation and plasticity that have been previously documented in fMRI learning paradigms (7). As seen in Fig 1, whereas HC showed significant adaptation in the hippocampus during encoding ($F_{1,6}$=25.22, p<.001, r^2=.81), such adaptation was absent in SCZ (p>.25). In contrast, similar patterns of adaptation were observed in the prefrontal cortex (r^2s > .69) in both groups.

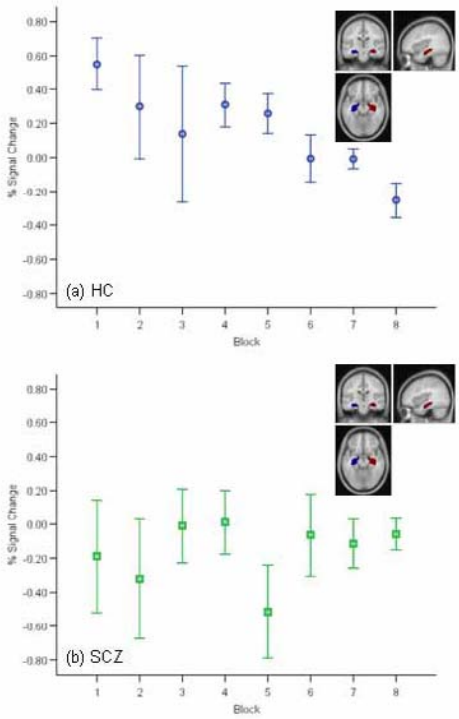

Figure 1. Changes in signal over time (block) from the hippocampus are plotted for HC (a) and SCZ (b). Adaptation of the hippocampal response observed in HC is absent in SCZ. Error bars are ± sem.

Discussion: Hippocampal and frontal hypoactivity, combined with hippocampal dysplasticity may characterize functional deficits in SCZ in associative learning. These results may be plausibly related to the dysfunction of specific neurotransmitter systems in SCZ. Associative learning depends on synaptic coincidence detection (8), which is in turn facilitated by *N*-methyl-D-aspartate (NMDA) receptor sensitivity (9). Increased NMDA receptor sensitivity results in superior associative memory (10); depleted sensitivity leads to impaired associative memory (11). Recent work proposes that SCZ may be characterized by loss of synaptic plasticity resulting from abnormal interactions between NMDA and glutamatergic transmission systems (12, 13). Our results suggest that systems neuroscience may help identify putative functional signatures of such pharmacologic dysfunction, and may in the future provide robust markers of pharmacologic efficacy in chronic SCZ.

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